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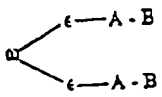
(54) Title: DP-IV-SERINE PROTEASE INHIBITORS

A-B (Groups I and II)



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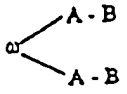

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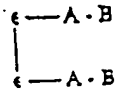
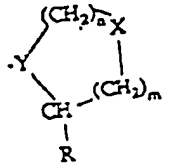


(3)

(Group III)



(4)

(57) Abstract

Compounds selected from those of general formula [A-B (Groups I and II)] and (group III), (1, 2 and 3) where B is (4) and A is selected from specified aminoacyl compounds are inhibitors of DP-IV mediated processes.

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DP-IV-SERINE PROTEASE INHIBITORS

Background

DP-IV (EC 3.4.14.5) is a membrane-bound serine protease first identified in rat kidney by its ability to cleave dipeptides from the N-terminus of certain peptides (Hopsu-Havu, V.K. and Glenner, G.G., *Histochemie*, 1966, 7, 197). The dipeptides must be of the type X-Pro or X-Ala where X = any amino acid. X-Proline is more efficiently cleaved than X-Ala.

DP-IV is widely distributed in mammalian tissues and is found in great abundance in the kidney, intestinal epithelium and placenta (Yaron, A. and Naider, F., *Critical Reviews in Biochem. Mol. Biol.* 1993, 28 (1), 31). In the human immune system the enzyme is expressed almost exclusively by activated T-lymphocytes of the $CD4^+$ type where the enzyme has been shown to be synonymous with the cell-surface antigen CD26.

The exact role of DP-IV in human physiology is not completely understood but recent research has shown that the enzyme clearly has a major role in human physiology and pathophysiology, eg.

(a) The immune response: DP-IV expression is increased in T-cells upon mitogenic or antigenic stimulation (Mattern, T. et al., *Scand. J. Immunol.* 1991, 33, 737). It has been reported that inhibitors of DP-IV and antibodies to DP-IV suppress the proliferation of mitogen- and antigen-stimulated T-cells in a dose-dependant manner (Schön, E. et al., *Biol. Chem. Hoppe-Seyler*, 1991, 372, 305 and refs. within).

Various other functions of T-lymphocytes such as cytokine production, IL-2 mediated cell proliferation and B-cell helper activity have been shown to be dependant on DP-IV activity (Schön, E. et al., *Scand. J. Immunol.* 1989, 29, 127). Recently, DP-IV inhibitors based on boroproline where reported (Flentke, G.R. et al., *Proc. Natl. Acad. Sci. USA*, 1991, 88, 1556) which, although unstable, were effective in inhibiting antigen-induced lymphocyte proliferation and IL-2 production in murine $CD4^+$ T-helper cells. Such boronic acid inhibitors have been shown to have an effect in vivo in mice causing suppression of antibody production induced by immune challenge (Kubota, T. et al., *Clin. Exp. Immunol.* 1992, 89, 192). Other recent papers also provide evidence for the involvement of DP-IV in the immune response (eg. Tanaka, T. et al., *Proc. Natl. Acad. Sci. NY*, 1993, 90, 4586; Hegen, M. et al., *Cell Immun.* 1993, 146, 249; Subramanyan, M. et al., *J. Immunol.* 1993, 150, 2544).

The importance of DP-IV is attributed by some investigators to its cell-surface association with the transmembrane phosphatase CD45 (Torimoto, Y. et al., *J. Immunol.* 1991, 147, 2514). The CD45 - DP-IV association is possibly disrupted by DP-IV inhibitors or non-active site ligands. CD45 is known to be an integral component of T-cell signalling.

(b) Recently, a press release from the Pasteur Institute in Paris (and subsequently a presentation by A.G. Hovanessian at the 8th Cent. Gardes Meeting, Paris, 25-27th October 1993) reported that DP-IV was essential for the penetration and infectivity of HIV-1 and HIV-2 viruses in $CD4^+$ T-cells. The French group claimed that DP-IV interacted with and may have cleaved the V3 loop of the gp120 envelope glyco-protein of the virus. They also reported that inhibitors or antibodies to DP-IV successfully prevented entry of the virus into cells. It was known previously that there is a selective decrease of CD26 expression in T-cells from HIV-1 infected individuals (Valle-Blazquez, M. et al., *J. Immunol.* 1992, 149, 3073), and that HIV-1 Tat protein binds to DP-IV (Subramanyam, M. et al., *J. Immunol.* 1993, 150, 2544).

(c) It has been shown recently that lung endothelial DP-IV is an adhesion molecule for lung-metastatic rat breast and prostate carcinoma cells (Johnson, R.C. et al., *J. Cell. Biol.* 1993, 121, 1423). DP-IV is known to bind to fibronectin and some metastatic tumour cells are known to carry large amounts of fibronectin on their surface.

(d) DP-IV has been shown to associate with the enzyme adenosine deaminase (ADA) on the surface of T-cells (Kameoka, J. et al., *Science*, 1993, 261, 466). ADA deficiency causes severe combined immunodeficiency disease (SCID) in humans. This ADA-CD26 interaction may provide clues to the pathophysiology of SCID.

(e) High levels of DP-IV expression have been found in human skin fibroblast cells from patients with psoriasis, rheumatoid arthritis (RA) and lichen planus (Raynaud, F. et al., *J. Cell. Physiol.* 1992, 151, 378).

(f) High DP-IV activity has been found in tissue homogenates from patients with benign prostate hypertrophy and in prostatosomes. These are prostate derived organelles important for the enhancement of sperm forward motility (Vanhoof, G. et al., *Eur. J. Clin. Chem. Clin. Biochem.* 1992, 30, 333).

(g) DP-IV has been shown to be responsible for the degradation and inactivation of circulating peptides with penultimate proline or alanine at the N-terminus, eg. substance P, growth hormone releasing factor and members of the glucagon/vasoactive intestinal peptide family (Menthein, R. et al., *Eur. J. Biochem.* 1993, 214, 829).

(h) Raised levels of DP-IV have been observed in the gingiva of patients with periodontitis (Cox, S.W. et al., *Arch. Oral. Biol.* 1992, 37, 167).

(i) There are also a number of other reports of raised (or sometimes lowered) levels of DP-IV in various pathological conditions.

It follows from the above that potent inhibitors of DP-IV may be useful as drugs for the treatment of human disease. Such inhibitors could be useful as:

(a) Immunosuppressants, eg. in organ transplantation; cytokine release suppressants eg. in various autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, RA.

(b) Drugs for the prevention of HIV entry into T-cells and therefore useful in the prophylaxis and treatment of AIDS.

(c) Drugs for the prevention of metastases, particularly of breast and prostate tumours to the lungs.

(d) Agents to treat dermatological diseases, eg. psoriasis, lichen planus.

(e) Drugs to suppress sperm motility and therefore act as male contraceptive agents.

(f) Agents beneficial in benign prostate hypertrophy.

Inhibitors of DP-IV

The only competitive inhibitors of DP-IV enzyme activity reported so far are the unstable boronic acids ($t_{\frac{1}{2}}$ 30 - 90 min at pH 7) mentioned above. (Bachovchin et al., WO 91/16339, October 1991) having K_i values in the nanomolar range for DP-IV, and simple amino-acid pyrrolidides or thiazolides (Neubert et al., DD 296 075 A5, November 1991) which have only modest potency ($K_i > 0.1$ μM). Amino-acyl proline aldehydes claimed in the same German patent cannot be synthesised due to a facile intramolecular condensation of the N-terminal amino group with the aldehyde function.

We now disclose highly potent competitive inhibitors of DP-IV (with K_i values in the 10^{-6} - 10^{-10} range) which are also chemically stable ($t_{\frac{1}{2}}$ > 24 h). They fall into three broad groups of compounds (Groups I, II and III).

GROUP I

These are molecules designed to bind tightly in the active site of DP-IV and to inhibit its proteolytic activity without interfering with attachment of any accessory ligands which may bind to the surface of DP-IV (i.e. not at its active site). Such Group I compounds could be useful as immunosuppressants; anti-HIV infectivity agents; agents to suppress release of certain cytokines (eg. IL-2, IL-6, γ-INF) from activated T-cells. The boronic acids and pyrrolidides referred to earlier also fall into this category.

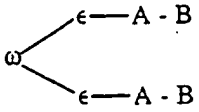
GROUP II

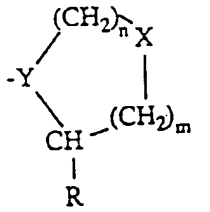
These are evolved from Group I compounds; however they contain long-chain extensions to the side-chains of the amino-acid defined as A in the general structure. The resulting compounds bind tightly to the active-site of DP-IV but the long-chain extensions protrude from the enzyme active site and serve to prevent the attachment of any other ligand which may bind to the surface of DP-IV. Such compounds could have the same uses as Group I compounds but in addition could block the interaction of DP-IV with (i) CD45 (ii) the gp 120 V3 loop of HIV-1 (iii) tumour cell surface fibronectin (iv) any other ligand important for T-cell activation, virus entry into T-cells or tumour cell adhesion.

GROUP III

This group comprises novel dimers in which two active-site directed inhibitors of DP-IV are linked via the side-chains of their amino-acid residues designated A in the general structure by a long chain. Such dimers can inhibit two molecules of DP-IV concurrently and also prevent accessory ligands binding to the surface of DP-IV. These dimers would have the same uses as Group II compounds but may be more effective.

The invention provides inhibitors of DP-IV mediated processes, the inhibitors being of general formula:

A-B (Groups I and II) or  (Group III)

where B is  ;

n = 1 or 2;
m = 0, 1 or 2;
X = CH_2, O, S, SO, SO_2, NH or NR_1 where R_1 = lower alkyl (C_1 to C_6);

A is attached to Y;
-Y = -N, -CH or =C (when the -CO group of A is replaced with CH= or CF=);
R = H, CN, CHO, $B(OH)_2$, $C\equiv C\text{-}R_7$, or $CH{=}N\text{-}R_8$;
R_7 = H, F, lower alkyl (C_1 to C_6), CN, NO_2, OR_9, CO_2R_9 or COR_9;

R_8 = Ph, OH, OR_9, $OCOR_9$, or OBn;
R_9 = lower alkyl (C_1 - C_6); and either ω or both ϵ's may be absent.

The structure of A is dependent on the nature of R in moiety B and on the nature of the group to which the resulting compound belongs.

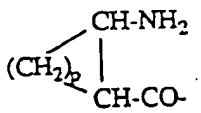
Group I Compounds

(a) R = H

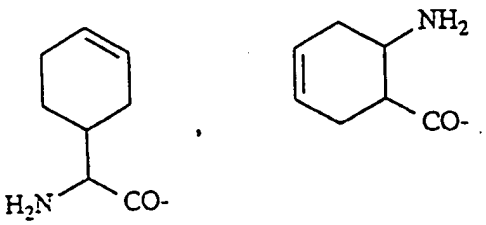
A is an α-amino-acyl group derived from an α-amino-acid bearing a cycloaliphatic side-chain (e.g. C_4 to C_{10}, mono or bicyclic) whose ring may contain one or more heteroatoms e.g. L-cyclohexylglycine, L-cyclopentylglycine, L-decahydro-naphthylglycine, L-piperidylglycine;

or

A is a β-amino-acyl group of general formula

 where p = 1 - 6 and the ring may also contain one or more heteroatoms replacing CH_2 unit(s).

Both α and β-amino acyl groups in (a) above may contain unsaturation in their rings e.g.



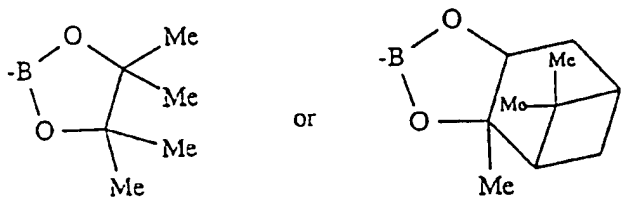
and also may contain one or more heteroatoms.

(b) R = CN: C≡C-R_7 or CH=N-R_8

A is as defined in (a) above but in addition may be derived from any L-α-amino acid bearing a lipophilic side-chain, eg. Ile.

(c) R = CHO or $B(OH)_2$

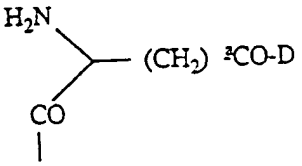
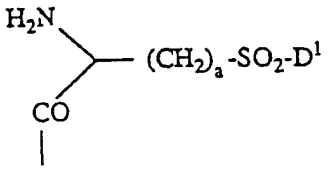
A is a β-amino-acyl group as defined in (a) above. The resulting A-B compounds are stable, unlike α-aminoacyl derivatives of the same type which undergo a facile intramolecular cyclisation. In compounds (c) $B(OH)_2$ may be present as a boronate ester eg.



these being labile in water giving the free boronic acids.

Group II Compounds

Where R = H, CN, C≡C-R_7 or CH=N-R_8, A is an α-amino acid derivative whose side-chain carries a functional group which is derivatised to produce a long chain terminating in various groups R_3. A may be of the following three types of structure:

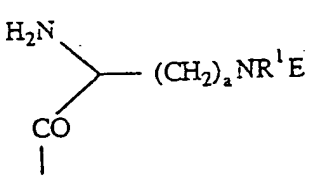
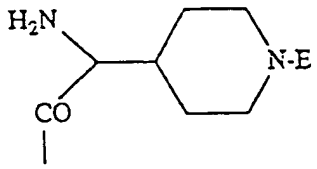
(i)  or 

where a = 1 - 5; D = G-$(CH_2)_b$-$(R_4)_q$-R_3; G = O, NH, or NMe;
b = 0-12; q = 0-5;

D^1 = D with G ≠ O;

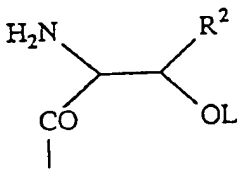
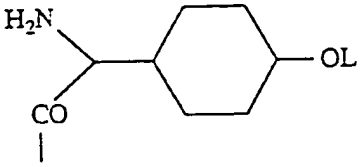
R_4 = Z-NH-$(CH_2)_c$- or NH-Z-$(CH_2)_c$- where c = 1-12 and Z = CO, CH_2 or SO_2; and

R_3 = CO_2H or ester [e.g. any lower alkyl, fluoroalkyl or cycloalkyl (C_1 to C_8), or aromatic or heteroaromatic (5 or 6-membered rings, mono- or bicylic) ester] thereof; $CONH_2$; $CONHNH_2$; $CONR_5R_6$; $CONHNR_5R_6$; PO_3H (or ester thereof e.g. as defined under CO_2H); SO_3H; SO_2NH_2; $SO_2NR_5R_6$; OH; OR_5; aryl or heteroaryl (e.g. 5 or 6-membered rings, monocyclic or bicyclic) [including substituted aryl or heteroaryl with substituents preferably chosen from F, Cl, I, Br, OH, OR_5, NO_2, SO_3H, SO_2NH_2, $SO_2NR_5R_6$, NH_2, NR_5R_6, CO_2R_5, CF_3, CN, $CONH_2$, $CONR_5R_6$, $NHCO_2R_5$, $CH(:NR_5)NR_5R_6$, NH-$CH(:NR_5)NR_5R_6$ and R_5]; NH_2; NR_5R_6; $NHCO_2R_5$; $NHSO_2NR_5R_6$; $NHCOR_5$; NH-SO_2R_5; NH-$CH(:NR_5)NR_5R_6$; $NHCONR_5R_6$; sugar (which may be attached via an ether or a glycosidic bond); CO-aminosugar (attached via the -NH_2) eg. glucosamine or galactosamine; NHCO-aminosugar; or NHCS-aminosugar.
In the above definition of R_3 "sugar" refers to any carbohydrate or oligosaccharide, and R_5 and R_6 are independently selected from H and alkyl, fluoroalkyl and cycloalkyl groups (of up to 8 atoms), aryl, heteroaryl and alkylheteroaryl groups (of up to 11 atoms) or R_5 and R_6 together comprise a chain and (C_2 to C_8).

(ii)  or 

where R^1 = H, Me; the ring may also contain more heteroatoms;

E = J-$(CH_2)_b$-$(R_4)_q$-R_3; J = CO, CH_2 or SO_2; and a, b, q, R_3 and R_4 as defined under (i)

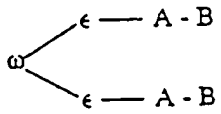
(iii)  or 

where R^2 = H or Me; the ring may also contain one or more heteroatoms;

L = $(CH_2)_d$-$[CO]_r$-$(CH_2)_b$-$(R_4)_q$-R_3 or $(CH_2)_e$-NR^1-$(CH_2)_b$-$(R_4)_q$-R_3;
r = 0 or 1; d = 0 - 4; e = 2 - 4; and b, q, R_3 and R_4 as defined under (i).

Group III

Group III compounds are defined by the general formula:

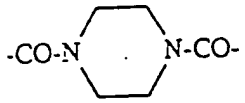


where ω = CH_2, O, NH, CO, S, SO_2, Ph or NMe and, independently,
ϵ = CH_2, O, NH, CO, S, SO_2, Ph or NMe.

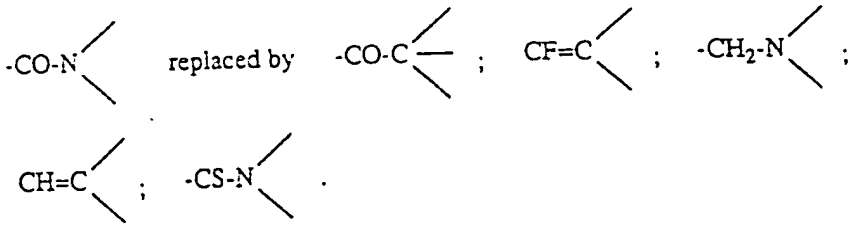
These compounds are symmetrical dimers. They may have any B structure as defined previously. A may be chosen from any group II structure [(i), (ii) or (iii)], but in this case the terminal group R_3 in each A residue is deleted and replaced with a shared symmetrical group [ϵ-ω-ϵ] which connects the two halves of the dimer; ω may be absent, in which case both ϵ's are joined together to constitute the chain linking the two A-B moieties; alternatively both ϵ's may be absent in which case ω solely joins the two A-B moieties.

The structure of ϵ-ω-ϵ must of course be chemically feasible eg. NH-CO-NH, CO-NH-CO-, SO_2-NMe-SO_2; it will be obvious to those skilled in the art which structures are not feasible, eg. -NH-NH-NH-. A specific possible example is shown in Table 7.

In such compounds as described under Groups II and III certain $-CH_2-$ groups present in the long chains could be replaced with known bioisosteres eg. -O- without affecting inhibitory or binding activity towards DP-IV. Also such groupings as $-CONHCH_2CH_2NHCO$ if they occur could be replaced by eg.



Further, for compounds in Groups I, II and III any amide bond connecting A and B or any amide in the side-chains of A (in Groups II and III) may be replaced by known bioisosteres of amides eg.



See Table 8 for examples of such replacements.

Biochemistry

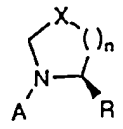
All compounds were tested *in vitro* against pure human DP-IV (purchased from M & E, Copenhagen, Denmark). Inhibition of DP-IV was determined using the fluorescent substrate Ala-Pro-AFC (K_m 0.8 μM) at three concentrations for each inhibitor. A typical assay (total volume 0.4 ml) comprised sodium Hepes 83.3 mM, EDTA 1.67 mM, BSA 1.5 mg ml^{-1} pH 7.8, DP-IV 25 μU ml^{-1}, inhibitor (in 10 mM acetate pH 4.0). The reaction was started by the addition of substrate and readings taken every 30 s for 7.5 min, excitation at 395 nm, emission 450 nm. K_i values were determined using Dixon plots.

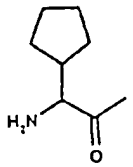
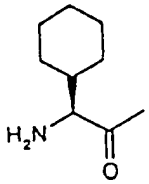
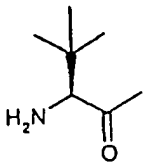
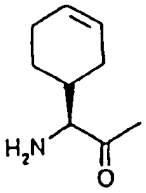
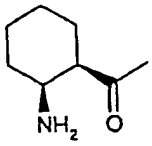
Chemistry

152 Examples of compounds synthesised are shown in Tables 1 - 8 followed by schemes and experimental details for the preparation of different structural types. All final products were characterised by FAB mass spectrometry and purity assessed by reverse phase hplc; all intermediates were characterised by ^{1}H NMR.

Table 9 shows selected K_i values against DP-IV determined for inhibitors of different structural types.

Table 1
Examples of Group I (a)



No.	A	X	R	n	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
1		CH_2	H	1	$C_{11}H_{20}N_2O$	196.2	197.2
2		CH_2	H	1	$C_{12}H_{22}N_2O$	210.2	211.2
3		CH_2	H	1	$C_{10}H_{20}N_2O$	184.2	185.2
4		CH_2	H	1	$C_{12}H_{20}N_2O$	208.2	209.2
5 *cis*		CH_2	H	1	$C_{11}H_{20}N_2O$	196.1	197.2

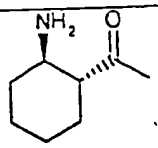
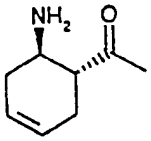
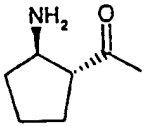
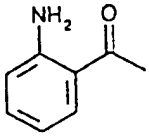
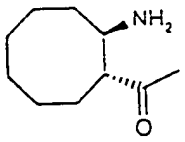
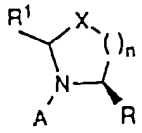
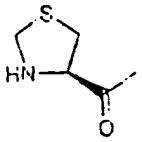
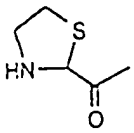
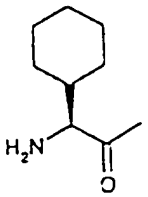
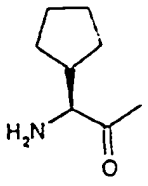
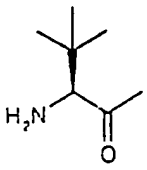
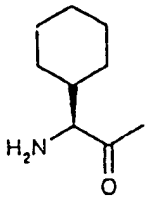
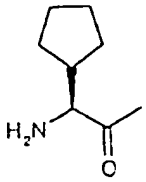
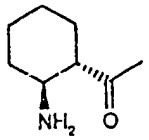
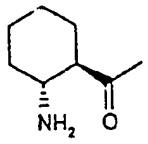
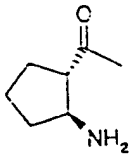
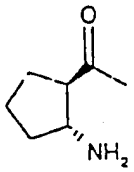
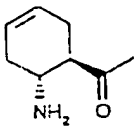
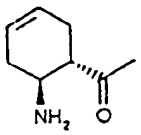
No.	A	X	R	n	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
6 *trans*		CH_2	H	1	$C_{11}H_{20}N_2O$	196.1	197.2
7 *trans*		CH_2	H	1	$C_{11}H_{18}N_2O$	194.1	195.2
8 *trans*		CH_2	H	1	$C_{10}H_{18}N_2O$	182.1	183.2
9		CH_2	H	1	$C_{11}H_{14}N_2O$	190.1	191.2
10 *trans*		CH_2	H	1	$C_{13}H_{24}N_2O$	224.2	225.2

Table 2
Examples of Group I (b)



No.	A	X	n	R^1	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
11	H-Ile	CH_2	1	H	CN	$C_{11}H_{19}N_3O$	209.3	210.2
12	H-Lys(Z)	CH_2	1	H	CN	$C_{19}H_{25}N_4O_3$	358.2	359.2
13	H-Pro	CH_2	1	H	CN	$C_{10}H_{15}N_3O$	193.1	194.1
14		CH_2	1	H	CN	$C_9H_{13}N_3OS$	211.1	212.2
15		CH_2	1	H	CN	$C_9H_{13}N_3OS$	211.1	212.2
16		CH_2	1	H	CN	$C_{13}H_{21}N_3O$	235.2	236.3
17		CH_2	1	H	CN	$C_{12}H_{19}N_3O$	221.2	222.2

No.	A	X	n	R^1	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
18		CH_2	1	H	CN	$C_{11}H_{19}N_3O$	209.2	210.2
19	H-Ile	S	1	H	CN	$C_{10}H_{17}N_3OS$	227.1	228.1
20	H-Ile	S	1	CN	H	$C_{10}H_{17}N_3OS$	227.1	228.1
21		S	1	H	CN	$C_{12}H_{19}N_3OS$	253.1	254.1
22	H-Lys(Z)	S	1	H	CN	$C_{18}H_{24}N_4O_3S$	376.2	377.2
23		S	1	H	CN	$C_{11}H_{17}N_3OS$	239.1	240.2
24	H-Ile	O	1	H	CN	$C_{10}H_{17}N_3O_2$	211.1	212.2
25	H-Ile	CH_2	2	H	CN	$C_{12}H_{21}N_3O$	223.2	224.2
26	H-Ile	S	2	H	CN	$C_{11}H_{19}N_3OS$	241.1	242.1
27	H-Ile	SO_2	1	H	CN	$C_{10}H_{17}N_3O_3S$	259.1	260.1
28	H-Ile	$S^+\cdots O^-$	1	H	CN	$C_{10}H_{17}N_3O_2S$	243.1	244.1
29	H-Ile	S^+-O^-	1	H	CN	$C_{10}H_{17}N_3O_2S$	243.1	244.2

No.	A	X	n	R^1	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
30		CH_2	1	H	CN	$C_{12}H_{19}N_3O$	221.2	222.2
31		CH_2	1	H	CN	$C_{12}H_{19}N_3O$	221.2	222.2
32		CH_2	1	H	CN	$C_{11}H_{17}N_3O$	207.2	208.2
33		CH_2	1	H	CN	$C_{11}H_{17}N_3O$	207.2	208.2
34		CH_2	1	H	CN	$C_{12}H_{17}N_3O$	219.1	220.1
35		CH_2	1	H	CN	$C_{12}H_{17}N_3O$	219.1	220.1

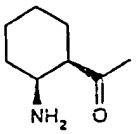
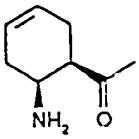
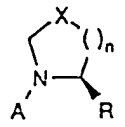
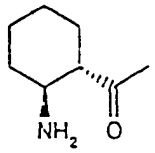
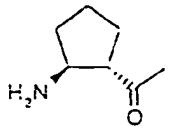
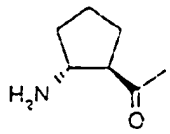
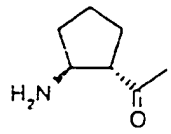
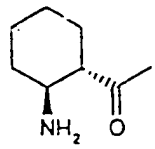
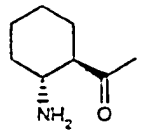
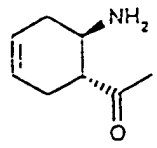
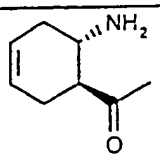
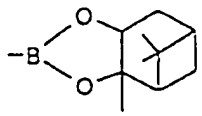
No.	A	X	n	R^1	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
36		CH_2	1	H	CN	$C_{12}H_{19}N_3O$	221.2	222.2
37		CH_2	1	H	CN	$C_{12}H_{17}N_3O$	219.1	220.1

Table 3
Examples of Group I (c)



No.	A	X	R	n	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
38		CH_2	CHO	1	$C_{12}H_{20}N_2O_2$	224.2	225.2
39		CH_2	CHO	1	$C_{11}H_{18}N_2O_2$	210.2	211.2
40		CH_2	CHO	1	$C_{11}H_{18}N_2O_2$	210.2	211.2
41		CH_2	B*	1	$C_{20}H_{33}BN_2O_3$	360.3	361.3
42		CH_2	B*	1	$C_{21}H_{35}BN_2O_3$	374.3	375.1
43		CH_2	B*	1	$C_{21}H_{35}BN_2O_3$	374.3	375.1
44		CH_2	B*	1	$C_{21}H_{33}BN_2O_3$	372.3	373.3

No.	A	X	R	n	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
45		CH_2	B*	1	$C_{21}H_{33}BN_2O_3$	372.3	373.3

B* = 

No.	n	Q	X	m	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
59	2	$-CONH(CH_2)_5CO_2Bn$	CH_2	1	H	$C_{22}H_{33}N_3O_4$	403.3	404.3
60	2	$-CONH(CH_2)_5CO_2H$	CH_2	1	H	$C_{15}H_{27}N_3O_4$	313.2	314.2
61	2	$-CONH(CH_2)_2CO_2H$	CH_2	1	H	$C_{12}H_{21}N_3O_4$	271.2	272.2
62	2	$-CONH(CH_2)_7CO_2Bn$	CH_2	1	H	$C_{24}H_{37}N_3O_4$	431.3	432.4
63	2	$-CONH(CH_2)_7CO_2H$	CH_2	1	H	$C_{17}H_{31}N_3O_4$	341.3	342.5
64	2	$-CONH(CH_2)_7CONH-(CH_2)_3NHZ$	CH_2	1	H	$C_{29}H_{45}N_5O_5$	531.3	532.3
65	2	$-CONH(CH_2)_6CONH-(CH_2)_5CO_2Bn$	CH_2	1	H	$C_{29}H_{46}N_4O_5$	530.4	531.2
66	2	$-CONH(CH_2)_6CONH-(CH_2)_5CO_2H$	CH_2	1	H	$C_{22}H_{40}N_4O_5$	440.3	441.3
67	2	$-CONH(CH_2)_7CONH-(CH_2)_3NH_2$	CH_2	1	H	$C_{20}H_{39}N_5O_3$	397.3	398.3
68	2	$-CONH(CH_2)_{11}CO_2Bn$	CH_2	1	H	$C_{28}H_{45}N_3O_4$	487.3	488.4
69	2	$-CONH(CH_2)_{11}CO_2H$	CH_2	1	H	$C_{21}H_{39}N_3O_4$	397.3	398.3
70	2	$-CONH(CH_2)_6CO_2Bn$	CH_2	1	H	$C_{23}H_{35}N_3O_4$	417.3	418.3
71	2	$-CONH(CH_2)_6CO_2H$	CH_2	1	H	$C_{16}H_{29}N_3O_4$	327.2	328.2
72	2	$-CONH(CH_2)_5CONH-CH_2CF_3$	CH_2	1	H	$C_{17}H_{29}F_3N_4O_3$	394.2	395.3

No.	n	Q	X	m	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
73	2	-CONH$(CH_2)_5$CONH-$CH_2(CF_2)_2CF_3$	CH_2	1	H	$C_{19}H_{29}F_7N_4O_3$	494.2	495.2
74	2	-CONH$(CH_2)_5$CONH-$(CH_2)_6OH$	CH_2	1	H	$C_{21}H_{40}N_4O_4$	412.3	413.2
75	2	-CONH$(CH_2)_5$CONH-$(CH_2)_3Ph$	CH_2	1	H	$C_{24}H_{38}N_4O_3$	430.3	431.2
76	2	-CONH$(CH_2)_5$CONH-$(CH_2)_4Ph$	CH_2	1	H	$C_{25}H_{40}N_4O_3$	444.3	445.2
77	2	-CONH$(CH_2)_5$CON-$(^nBu)_2$	CH_2	1	H	$C_{23}H_{44}N_4O_3$	424.3	425.3
78	2	-CONH$(CH_2)_5$CON-$(^nHx)_2$	CH_2	1	H	$C_{27}H_{52}N_4O_3$	480.4	481.4
79	2	-CONH$(CH_2)_5$CONH-CH_2Ph	CH_2	1	H	$C_{22}H_{34}N_4O_3$	402.3	403.4
80	2	-CONH$(CH_2)_4CO_2Bn$	CH_2	1	H	$C_{21}H_{31}N_3O_4$	389.2	390.3
81	2	-CONH$(CH_2)_4CO_2H$	CH_2	1	H	$C_{14}H_{25}N_3O_4$	299.2	300.3
82	2	-CONH$(CH_2)_5$CONH-CH_2CH_3	CH_2	1	H	$C_{17}H_{32}N_4O_3$	340.3	341.3
83	2	-CONH$(CH_2)_6OH$	CH_2	1	H	$C_{15}H_{29}N_3O_3$	299.2	300.3
84	2	-CONH$(CH_2)_5$CO-1-Pip	CH_2	1	H	$C_{20}H_{36}N_4O_3$	380.3	381.4
85	2	-CONH$(CH_2)_5CONH_2$	CH_2	1	H	$C_{15}H_{28}N_4O_3$	312.2	313.3

No.	n	Q	X	m	R	Formula	Calculated Mol. Wt.	FAB Mass spec [M+H]+
86	2	-CONH$(CH_2)_5$CONH-$(CH_2)_9CH_3$	CH_2	1	H	$C_{25}H_{48}N_4O_3$	452.4	453.5
87	2	-CONH$(CH_2)_5$CONH-$(CH_2)_6CH_3$	CH_2	1	H	$C_{22}H_{42}N_4O_3$	410.3	411.4
88	2	-CONH$(CH_2)_5$CONH-CH_2Ch	CH_2	1	H	$C_{22}H_{40}N_4O_3$	408.3	409.4
89	2	-CONH$(CH_2)_5$CONH-$(CH_2)_3$NHZ	CH_2	1	H	$C_{25}H_{41}N_5O_5$	503.3	504.4
90	2	-CONH$(CH_2)_5$CONH-$(CH_2)_3NH_2$	CH_2	1	H	$C_{18}H_{35}N_5O_3$	369.3	370.3
91	2	-CONH$(CH_2)_5$CONH-$(CH_2)_3$-Gua	CH_2	1	H	$C_{19}H_{37}N_7O_3$	411.3	412.4
92	2	-CONH$(CH_2)_5$CONH-Ph(4-SO_3H)	CH_2	1	H	$C_{21}H_{32}N_4O_6S$	468.2	469.2
93	2	-CONH$(CH_2)_5$CONH-4-Pip(1-Bn)	CH_2	1	H	$C_{27}H_{43}N_5O_3$	485.3	486.3
94	2	-CONH$(CH_2)_5$CONH-4-Pip	CH_2	1	H	$C_{20}H_{37}N_5O_3$	395.3	396.3
95	2	-CONH$(CH_2)_4$N(Z)-$(CH_2)_3$NHZ	CH_2	1	H	$C_{32}H_{45}N_5O_6$	595.3	596.3
96	2	-CONH$(CH_2)_4$NH-$(CH_2)_3NH_2$	CH_2	1	H	$C_{16}H_{33}N_5O_2$	327.2	328.2

No.	n	Q	X	m	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
97	2	$-CONH(CH_2)_5CO_2Bn$	CH_2	1	CN	$C_{23}H_{32}N_4O_4$	428.3	429.3
98	3	$-CONH(CH_2)_6CONH-(CH_2)_5CO_2Bn$	CH_2	1	H	$C_{30}H_{48}N_4O_5$	544.4	545.2
99	3	$-CONH(CH_2)_6CONH-(CH_2)_5CO_2H$	CH_2	1	H	$C_{23}H_{42}N_4O_5$	454.3	455.3
100	3	$-CONH(CH_2)_5CO_2Bn$	CH_2	1	H	$C_{23}H_{35}N_3O_4$	417.3	418.2
101	3	$-CONH(CH_2)_5CO_2H$	CH_2	1	H	$C_{16}H_{29}N_3O_4$	327.2	328.2
102	2	$-SO_2NH(CH_2)_5CO_2H$	CH_2	1	H	$C_{14}H_{27}N_3O_5S$	349.2	350.2
103	2	$-CONH(CH_2)_6NH-G^*$	CH_2	1	H	$C_{24}H_{45}N_5O_7S$	547.4	548.5

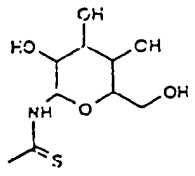
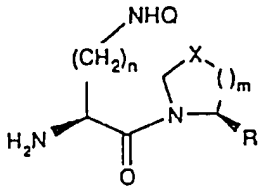
$G^* =$ 

Table 5
Examples of Group II (ii)

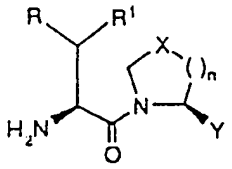


No.	n	Q	X	m	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
104	1	$-CO(CH_2)_6CO_2H$	CH_2	1	H	$C_{15}H_{27}N_3O_4$	313.2	314.3
105	1	$-CO(CH_2)_6CO_2Bn$	CH_2	1	H	$C_{22}H_{33}N_3O_4$	403.3	404.3
106	3	$-CO(CH_2)_4CO_2H$	CH_2	1	H	$C_{15}H_{27}N_3O_4$	313.2	314.3
107	3	$-CO(CH_2)_4CO_2Me$	CH_2	1	H	$C_{16}H_{29}N_3O_4$	327.2	328.3
108	4	$-CO(CH_2)_5NH_2$	CH_2	1	H	$C_{16}H_{32}N_4O_2$	312.3	313.3
109	4	$-CO(CH_2)_3NH_2$	CH_2	1	H	$C_{14}H_{28}N_4O_2$	284.2	285.2
110	4	$-CO(CH_2)_3NHSO_2Pfp$	CH_2	1	H	$C_{20}H_{27}F_5N_4O_4S$	514.2	515.2
111	4	$-CO(CH_2)_3NHCOPfp$	CH_2	1	H	$C_{21}H_{27}F_5N_4O_3$	478.2	479.2
112	4	$-CO(CH_2)_3NHSO_2-CH_2CF_3$	CH_2	1	H	$C_{16}H_{29}F_3N_4O_4S$	430.2	431.3
113	4	$-CO(CH_2)_{11}NHCO-(CH_2)_6NHZ$	CH_2	1	H	$C_{37}H_{63}N_5O_5$	657.5	658.6
114	4	$-CO(CH_2)_{11}NH-CO(CH_2)_6NH_2$	CH_2	1	H	$C_{29}H_{57}N_5O_3$	523.4	524.4

No.	n	Q	X	m	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
115	4	$-CO(CH_2)_5NHCO-(CH_2)_5NHCO(CH_2)_5-NHZ$	CH_2	1	H	$C_{36}H_{60}N_6O_6$	672.5	673.6
116	4	$-CO(CH_2)_5NHCO-(CH_2)_5NHCO(CH_2)_5-NH_2$	CH_2	1	H	$C_{28}H_{54}N_6O_4$	538.4	539.4
117	4	$-CO(CH_2)_3CO_2H$	CH_2	1	H	$C_{15}H_{27}N_3O_4$	313.2	314.3
118	4	$-CO(CH_2)_3CO_2Bn$	CH_2	1	H	$C_{22}H_{33}N_3O_4$	403.3	404.3
119	4	$-CO(CH_2)_5NH_2$	CH_2	1	H	$C_{17}H_{34}N_4O_2$	326.3	327.3
120	4	$-CO(CH_2)_7NH_2$	CH_2	1	H	$C_{19}H_{36}N_4O_2$	340.3	341.3
121	4	$-CO(CH_2)_{16}Me$	CH_2	1	H	$C_{28}H_{55}N_3O_2$	465.4	466.4
122	4	$-CO(CH_2)_5$-Gua	CH_2	1	H	$C_{18}H_{36}N_6O_2$	368.3	369.3
123	4	$-SO_2(CH_2)_7CH_3$	CH_2	1	H	$C_{18}H_{37}N_3O_3S$	375.3	376.3
124	4	$-CO(CH_2)_{11}NH_2$	CH_2	1	H	$C_{22}H_{44}N_4O_2$	396.4	397.4
125	4	$-COCH_2NHZ$	CH_2	1	H	$C_{20}H_{30}N_4O_4$	390.2	391.3
126	4	$-CO(CH_2)_2NHZ$	CH_2	1	H	$C_{21}H_{32}N_4O_4$	404.2	405.3
127	4	$-CO(CH_2)_3NHZ$	CH_2	1	H	$C_{22}H_{34}N_4O_4$	418.3	419.3
128	4	$-CO(CH_2)_2NH_2$	CH_2	1	H	$C_{12}H_{24}N_4O_2$	256.2	257.2

No.	n	Q	X	m	R	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
129	4	$-CO(CH_2)_5NHZ$	CH_2	1	H	$C_{24}H_{38}N_4O_4$	446.3	447.4
130	4	$-COCH_2$-Gua	CH_2	1	H	$C_{13}H_{26}N_6O_2$	298.2	299.3
131	4	$-CO(CH_2)_2NH_2$	CH_2	1	H	$C_{13}H_{26}N_4O_2$	270.2	271.3
132	4	$-CO(CH_2)_2$-Gua	CH_2	1	H	$C_{14}H_{28}N_6O_2$	312.2	313.3
133	4	$-CO(CH_2)_3$-Gua	CH_2	1	H	$C_{15}H_{30}N_6O_2$	326.3	327.3
134	4	$-CO(CH_2)_5$-Gua	CH_2	1	H	$C_{17}H_{34}N_6O_2$	354.3	355.3
135	4	$-CO(CH_2)_6NH_2$	CH_2	1	CN	$C_{18}H_{33}N_5O_2$	351.3	352.4
136	4	$-CO(CH_2)_7NH_2$	CH_2	1	CN	$C_{19}H_{35}N_5O_2$	365.3	366.3

Table 6
Examples of Group II (iii)



No.	R	R^1	X	n	Y	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
137	H	$-OCH_2CONH(CH_2)_5-CO_2H$	CH_2	1	H	$C_{15}H_{27}N_3O_5$	329.2	330.3
138	H	$-OCH_2CONH(CH_2)_5-CO_2Bn$	CH_2	1	H	$C_{22}H_{33}N_3O_5$	419.3	420.3
139	H	$-OCH_2CONH(CH_2)_4-CO_2Bn$	CH_2	1	H	$C_{21}H_{31}N_3O_5$	405.2	406.3
140	H	$-OCH_2CONH(CH_2)_4-CO_2H$	CH_2	1	H	$C_{14}H_{25}N_3O_5$	315.2	316.3
141	CH_3	$-OCH_3$	CH_2	1	H	$C_9H_{18}N_2O_2$	186.1	187.2
142	CH_3	$-OC_2H_5$	CH_2	1	H	$C_{10}H_{20}N_2O_2$	200.1	201.2
143	CH_3	$-O(CH_2)_5CH_3$	CH_2	1	H	$C_{14}H_{28}N_2O_2$	256.2	257.3
144	CH_3	$-OCH_2CONH(CH_2)_5-CO_2Bn$	CH_2	1	H	$C_{23}H_{35}N_3O_5$	433.3	434.3
145	CH_3	$-OCH_2CONH(CH_2)_5-CO_2H$	CH_2	1	H	$C_{16}H_{29}N_3O_5$	343.2	344.3

No.	R	R^1	X	n	Y	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
146	CH_3	$-OCH_2CONH(CH_2)_4-CO_2Bn$	CH_2	1	H	$C_{22}H_{33}N_3O_5$	419.2	420.3
147	CH_3	$-OCH_2CONH(CH_2)_4-CO_2H$	CH_2	1	H	$C_{15}H_{27}N_3O_5$	329.2	330.3

Table 7
Example of Group III

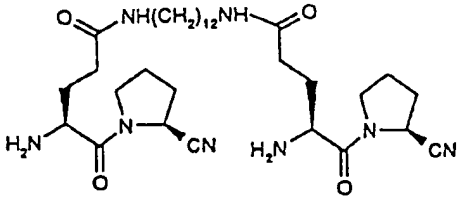
No.	Structure	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
148		$C_{32}H_{54}N_8O_4$	614.4	615.4

Table 8
Specific examples of compounds A-B, containing amide bond bioisosteres.

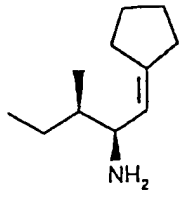
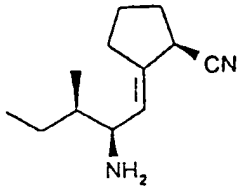
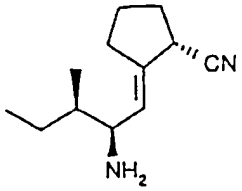
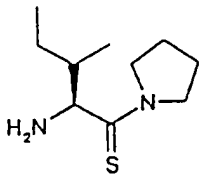
No.	A-B	Formula	Calculated Mol. Wt.	FAB Mass spec. $[M+H]^+$
149		$C_{11}H_{21}N$	167.2	168.2
150		$C_{12}H_{20}N_2$	192.2	193.2
151		$C_{12}H_{20}N_2$	192.2	193.2
152		$C_{10}H_{20}N_2S$	200.1	201.2

Table 9
Selected K_i values against DP-IV.

No.	K_i (M)
2	6.4×10^{-3}
7	7.6×10^{-6}
11	2.2×10^{-9}
20	1.7×10^{-9}
23	5.0×10^{-10}
35	3.7×10^{-3}
38	9.8×10^{-9}
44	2.0×10^{-9}
59	1.5×10^{-7}
66	1.8×10^{-7}
97	5.0×10^{-10}
110	2.5×10^{-7}
136	1.7×10^{-3}
143	9.4×10^{-7}
150	1.7×10^{-6}

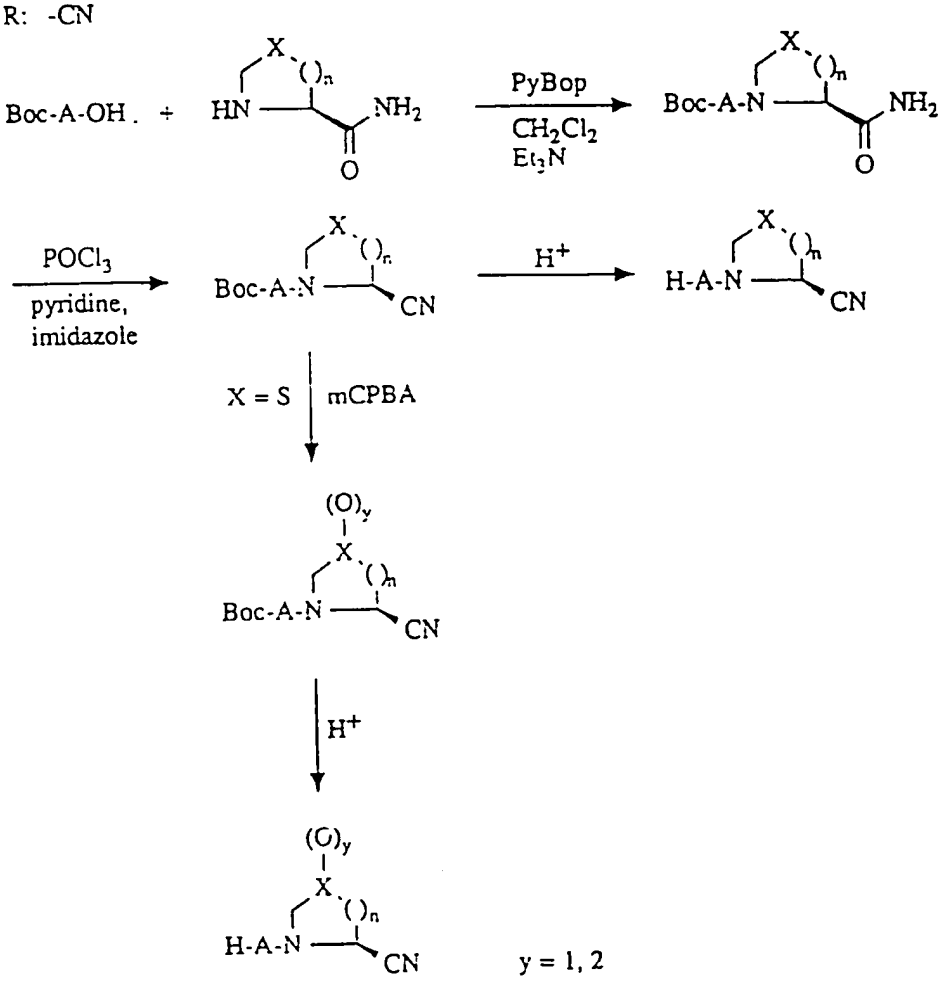
Schematic Representations for General Preparation of all Classes of Compounds

Table 1

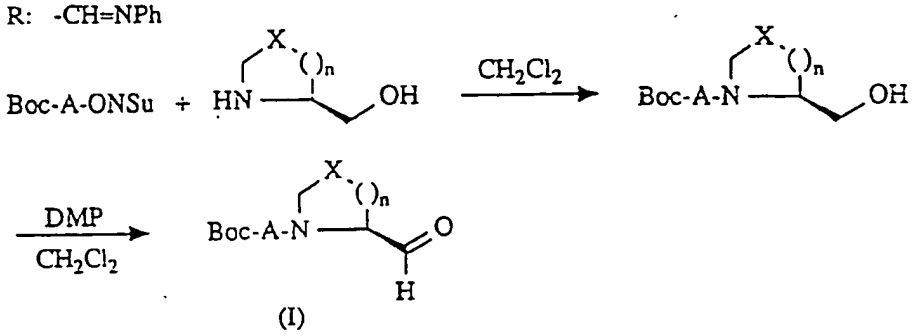
Compounds can be made by an adaption of the general route described by E. Schön et al., *Biol. Chem. Hoppe-Seyler*, 1991, *372*, 305-311.

Table 2

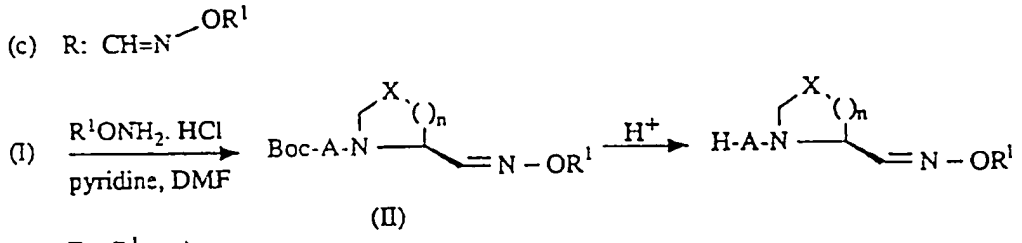
(a) R: -CN



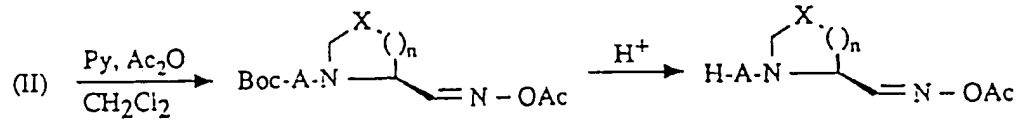
(b) R: -CH=NPh



(c) R: CH=N-OR^1



For R^1 = -Ac



(R^1 = H)

(d) R = -C≡CR

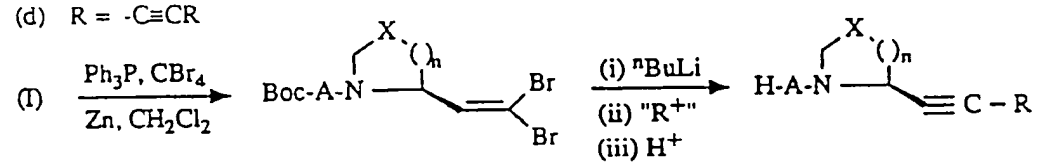
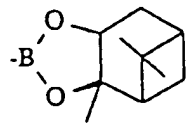


Table 3

(a) R = 

Prepared by method of: W.W. Bachovchin et al., *J. Biol. Chem.*, 1990, *265*, 3738-3743.

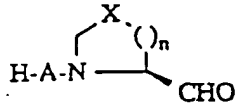
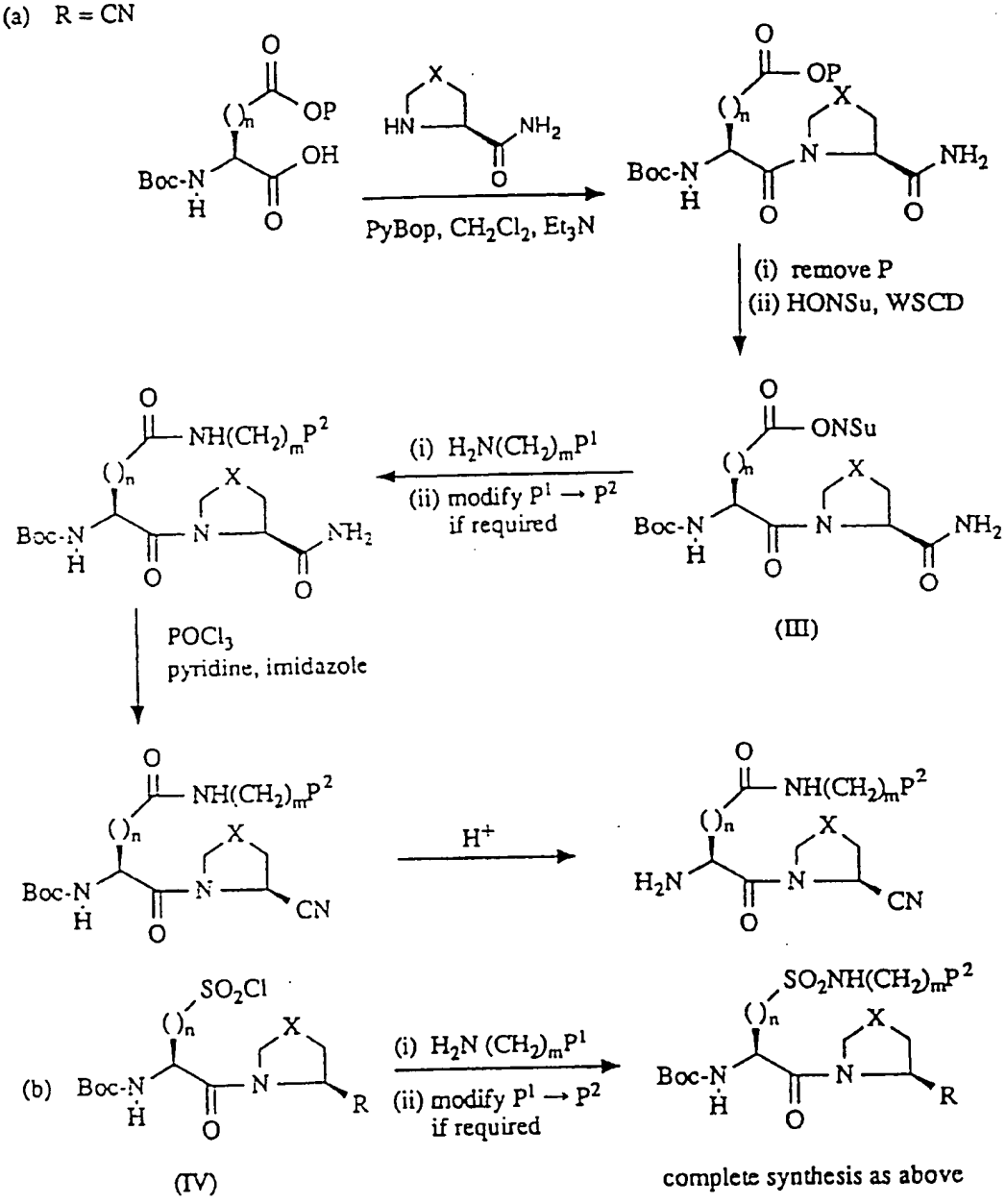
(b) R = CHO (I) $\xrightarrow{H^+}$ 

Table 4 (W, P = Protecting groups; P^1, P^2 = Groups as described in corresponding tables)

(a) R = CN



(b)

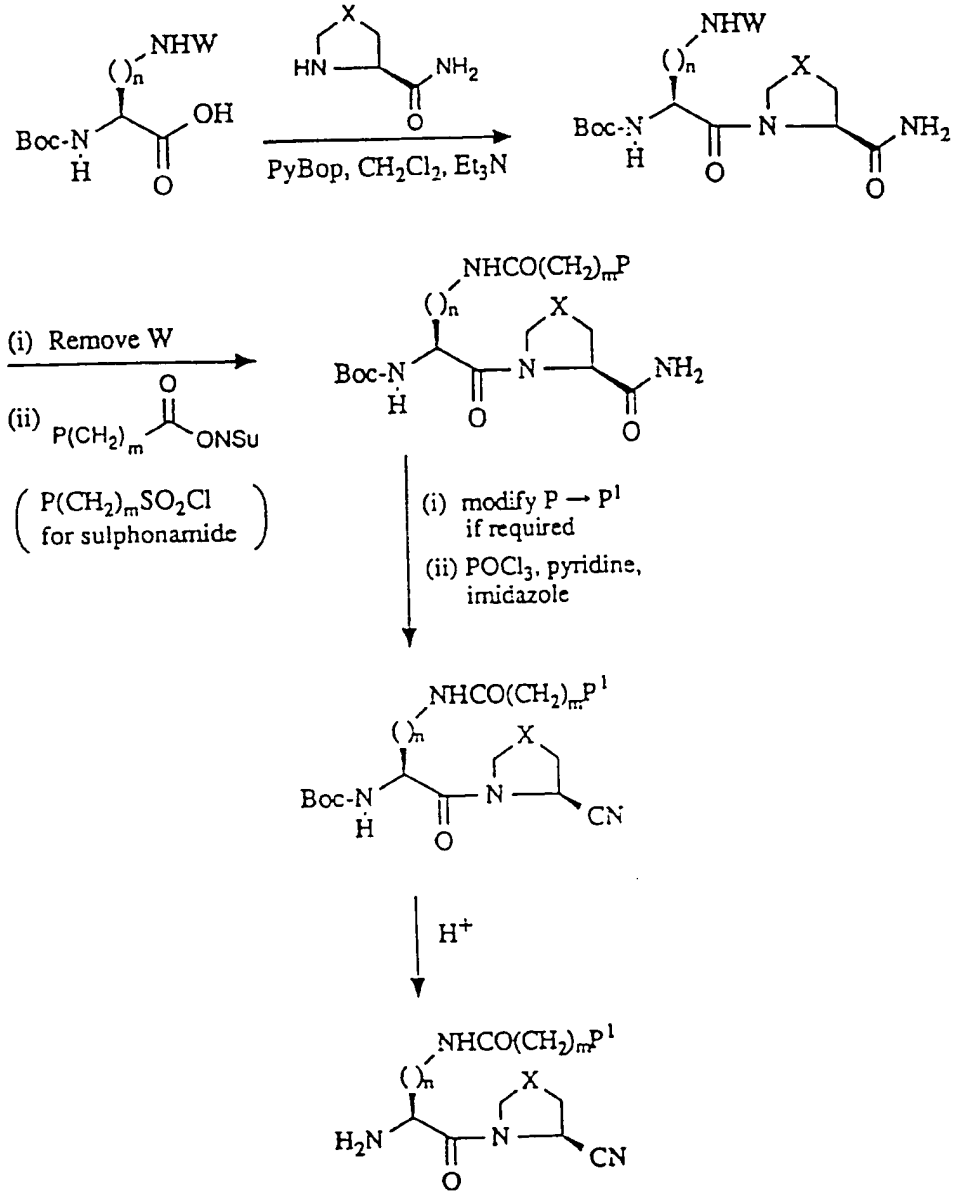
(IV) complete synthesis as above

(IV) was prepared via method of G. Luisi et al., *Tet. Lett.*, 1993, *34*, 2391-2392.

(c) For R = H, modify above procedure as described for Table 1 examples.

Table 5

(a) R = CN



(b) R = H, modify above procedure as described for Table 1 examples.

Table 6

Use method described for Table 5 examples for preparation of (VI) from (V)

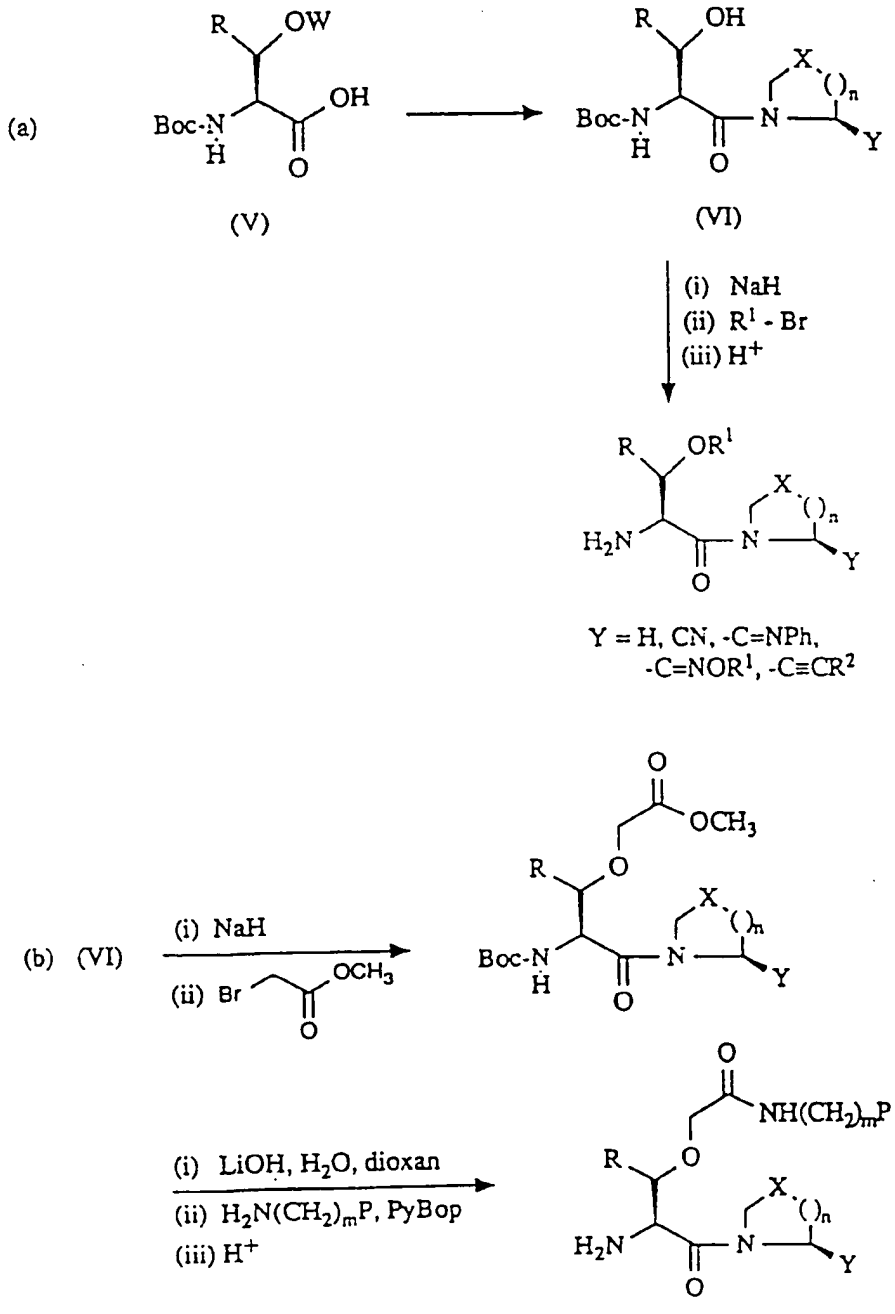


Table 7

Standard coupling, dehydration and deprotection sequence similar to above schemes.

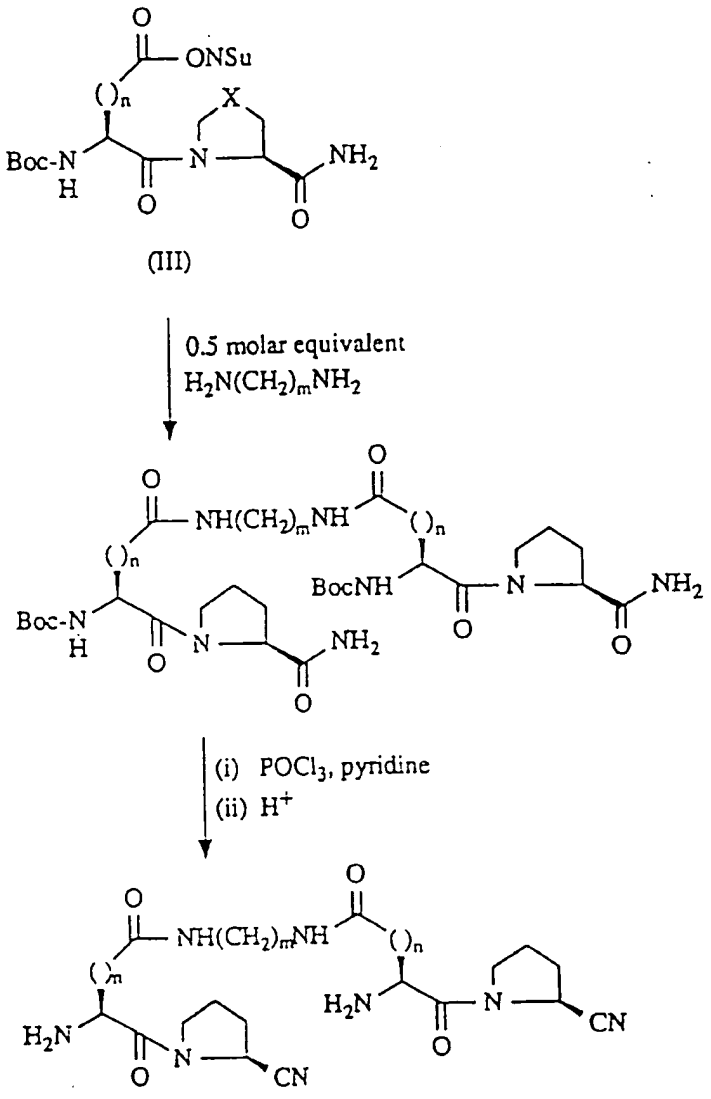
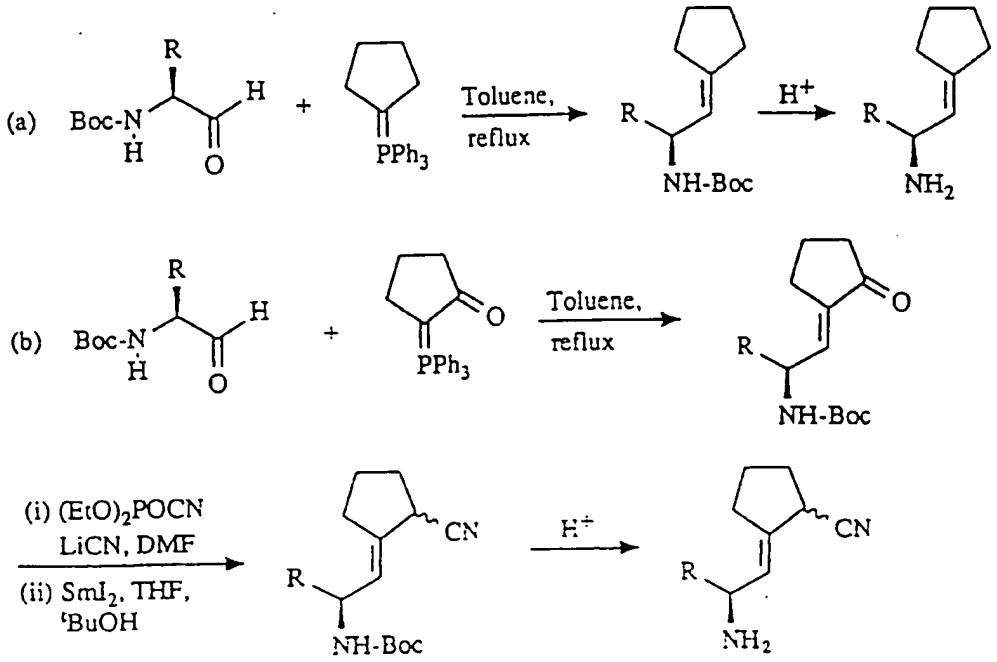


Table 8

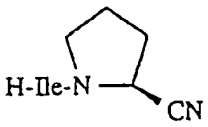


Thioamides were prepared by the method described by K. Clausen et al. *Tetrahedron*, 1981, *37*, 3635-3639. Other amide bioisosteres can be prepared from literature precedent. (A.F. Spatola in "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins", Vol. III, B. Weinstein Ed., Marcel Dekker, New York, 1983, p. 267).

Experimental Details for Specific Examples

EXAMPLE 1

2-(S)-Cyano-1-isoleucylpyrrolidine (11)



Di-isopropylethylamine was added to a solution of H-ProNH_2. HCl (225 mg, 1.50 mmol) in dry CH_2Cl_2 (15 cm^3) until the pH was adjusted to 9. BocIleONSu was added in one portion and the mixture stirred for 16 h, under a nitrogen atmosphere. The solvent was evaporated and the residue treated in the standard way, i.e. the residue was partitioned between ethyl acetate (60 cm^3) and 0.3 N $KHSO_4$ solution (10 cm^3). The organic layer was further washed with saturated $NaCHO_3$ solution (10 cm^3), water (10 cm^3) and brine (5 cm^3). The solution was dried (Na_2SO_4) and evaporated at reduced pressure. The crude product was passed down a short plug of silica gel, eluting with hexane:ethyl acetate, (10:90 to 0:100) to yield 301 mg (92%) of BocIleProNH_2 as a colourless foam.

^1H NMR ($CDCl_3$), δ (ppm); 6.90 (1H, br.s); 5.51 (1H, br.s); 5.18 (1H, d, J = 9.6 Hz); 4.62 (1H, dd, J = 2.6, 7.0 Hz); 4.29 (1H, dd, J = 8.4, 9.2 Hz); 3.79 - 3.58 (2H, m); 2.36 (1H, m); 2.09 - 1.57 (5H, m); 1.43 (9H, s); 1.17 (1H, m); 0.95 (3H, d, J = 6.6 Hz); 0.90 (3H, t, J = 7.3 Hz).

Imidazole (84 mg, 1.24 mmol) was added to a solution of BocIleProNH_2 in dry pyridine (10 cm^3), under a nitrogen atmosphere. The solution was cooled to -35°C, before the dropwise addition of $POCl_3$ (0.25 cm^3, 2.48 mmol). The reaction was stirred at -30°C to -20°C for 60 min. The solution was then evaporated and the crude residue subjected to column chromatography (silica gel) to yield 180 mg (94%) of 2-(S)-cyano-1-[N-(t-butoxycarbonyl) isoleucyl]pyrrolidine as a colourless oil.

^1H NMR ($CDCl_3$), δ (ppm); 5.14 (1H, d, J = 9.2 Hz); 4.80 (1H, dd, J = 2.6, 7.1 Hz); 4.22 (1H, dd, J = 7.9, 9.1 Hz); 3.81 (1H, m), 3.71 (1H, m), 2.30 - 2.12 (4H, m); 1.75 (1H, m); 1.60 (1H, m); 1.42 (9H, s); 1.19 (1H, m); 0.97 (3H, d, J = 6.9 Hz); 0.91 (3H, t, J = 7.3 Hz).

^{13}C NMR ($CDCl_3$), δ (ppm); 171.7, 155.6, 118.0, 79.6, 56.0, 46.5, 46.0, 37.8, 29.6, 28.1, 25.0, 24.2, 15.2, 10.9.

Deprotection was carried out by stirring with trifluoroacetic acid for 60 min. Evaporation and lyophilisation from water afforded 60 mg of 2-(S)-cyano-1-isoleucylpyrrolidine (11) as a white, fluffy solid.

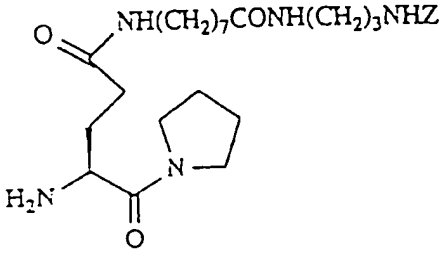
FAB Mass Spec: Calculated 209.3, Found $(M+H)^+ = 210.2$.

^1H NMR (D_2O), δ (ppm); 4.3 (1H, m); 3.64 (1H, d, J = 5.6 Hz); 3.16 (2H, m); 1.86 - 1.48 (5H, m); 0.98 (1H, m); 0.68 (1H, m); 0.51 (3H, d, J = 6.9 Hz); 0.38 (3H, t, J = 7.3 Hz).

^{13}NMR (D_2O), δ (ppm); 169.7, 119.7, 57.3, 48.6, 48.1, 36.9, 30.2, 25.8, 24.5, 15.4, 11.5.

EXAMPLE TWO

H-Glu[NH$(CH_2)_7$CONH$(CH_2)_3$NHZ]pyrrolidide (64)



Di-isopropylethylamine was added to a solution of BocGlu(OH)pyrrolidide (193 mg, 0.64 mmol) and PyBop (500 mg, 0.96 mmol) in CH_2Cl_2 (6 cm^3) to adjust the pH of the mixture to 9. After stirring for 5 min, a solution of benzyl 8-amino-octanoate (220 mg, 0.77 mmol) in CH_2Cl_2 (5 cm^3) was added. The mixture was stirred at room temp for 16 h. The reaction was worked up in the standard procedure as described in example one. The crude residue was subjected to column chromatography (1% to 3% methanol in ethyl acetate) to obtain 344 mg (99%) of BocGlu[NH$(CH_2)_7CO_2$Bn]pyrrolidide as a colourless solid.

^1H NMR ($CDCl_3$), δ (ppm); 7.35 (5H, s); 6.63 (1H, br.t, J = 6.7 Hz); 5.65 (1H, d, J = 8.3 Hz); 5.11 (2H, s); 4.36 (1H, dt, J = 2.6, 8.9 Hz); 3.55 - 3.20 (6H, m); 2.34 (2H, t, J = 7.3 Hz); 2.26 (2H, dd, J = 5.6, 7.3 Hz); 2.11 - 1.48 (10H, m); 1.43 (9H, s); 1.32 - 1.27 (6H, m).

Hydrogen gas was bubbled through a solution of BocGlu[NH$(CH_2)_7CO_2$Bn]pyrrolidide (230 mg, 0.43 mmol) in ethyl acetate (10 cm^3), containing 10% palladium on charcoal (50 mg). After 90 min, the reaction vessel was flushed with nitrogen, the solution filtered through a pad of celite and the solvent evaporated to yield 187 mg (98%) of BocGlu[NH$(CH_2)_7CO_2$H]pyrrolidide as a colourless oil.

Di-isopropylethylamine was added to a solution of BocGlu[NH$(CH_2)_7CO_2$H]pyrrolidide (125 mg, 0.28 mmol) and PyBop (221 mg, 0.43 mmol) in CH_2Cl_2 (10 cm^3) to adjust the pH of the solution to 9. After stirring for 5 min, a solution of ZNH$(CH_2)_3NH_2$. HCl (90 mg, 0.37 mmol) and di-isopropylethylamine (38 mg, 0.37 mmol) was added in one portion. The solution was stirred for 18 h then treated in the standard procedure as described for example one. The crude residue was subjected to column chromatography (2% to 15% methanol in ethyl acetate) to afford 151 mg (85%) of BocGlu[NH$(CH_2)_7$CONH$(CH_2)_3$NHZ]pyrrolidide as a colourless oil.

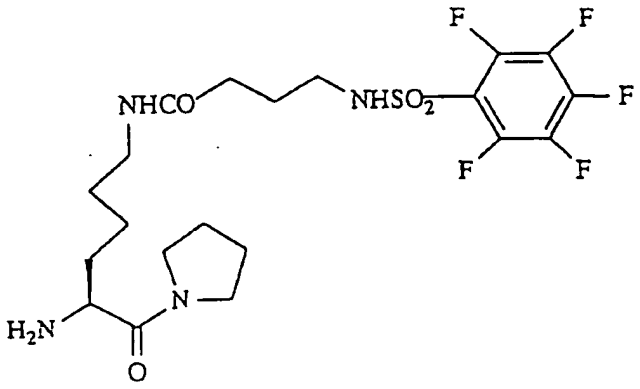
^{1}H NMR ($CDCl_3$), δ (ppm); 7.35 (5H, s); 6.60 (1H, br.t, J = 7.2 Hz); 6.14 (1H, br.t, J = 7.2 Hz); 5.63 (1H, d, J = 8.3 Hz); 5.39 (1H, br.t, J = 5.6 Hz); 5.10 (2H, s); 4.38 (1H, dt, J = 2.3, 9.2 Hz); 3.52 - 3.13 (10H, m); 2.26 (2H, t, J = 6.9 Hz); 2.17 (2H, t, J = 7.6 Hz); 1.98 - 1.48 (12H, m); 1.44 (9H, s); 1.38 - 1.23 (6H, m).

A solution of BocGlu[NH$(CH_2)_7$CONH$(CH_2)_3$NHZ]pyrrolidide (14 mg, 0.022 mmol) in 4N HCl/dioxan was stirred for 45 min. The solvent was evaporated and the residue dissolved in water, filtered and lyophilised to yield 13 mg of H-Glu[NH$(CH_2)_7$CONH$(CH_2)_3$NHZ]pyrrolidide (64) as a colourless oil.

FAB Mass Spec: Calculated 531.3, Found $(M+H)^+$ = 532.3.

EXAMPLE THREE

H-Lys[$CO(CH_2)_3NHSO_2Pfp$]pyrrolidide (110)



$ZNH(CH_2)_3CO_2NSu$ (570 mg, 1.7 mmol) was added in one portion to a solution of 1-[N-(t-butoxycarbonyl)lysyl]pyrrolidine (745 mg, 2.2 mmol) in dry CH_2Cl_2. The pH was adjusted to 9 with di-isopropylethylamine and the mixture stirred for 60 min. The solvent was evaporated and the residue treated in the standard procedure as described for example one. Column chromatography (100% ethyl acetate to 15% methanol in ethyl acetate) afforded 620 mg (68%) of BocLys[$CO(CH_2)_3NHZ$]pyrrolidide.

^{1}H NMR ($CDCl_3$), δ (ppm): 7.42 (5H, s); 6.31 (1H, br.t, J = 6.5 Hz); 5.58 (1H, d, J = 8.9 Hz); 5.39 (1H, br.t, J = 6.9 Hz); 5.17 (2H, s); 4.44 (1H, m); 3.72 - 3.20 (8H, m); 2.29 (2H, t, J = 7.3 Hz); 2.14 - 1.83 (8H, m); 1.78 - 1.41 (4H, m); 1.43 (9H, s).

Hydrogen gas was bubbled through a mixture of BocLys[$CO(CH_2)_3NHZ$]pyrrolidide (620 mg, 1.16 mmol) and 10% palladium on charcoal in methanol (10 cm^3) containing one molecular equivalent of 2N HCl. After 60 min, the reaction was flushed with nitrogen, and filtered through celite. Evaporation of the solvent afforded 282 mg (49%) of BocLys[$CO(CH_2)_3NH_2$. HCl]pyrrolidide. This product was dissolved in CH_2Cl_2 (10 cm^3) and stirred, under a nitrogen atmosphere. Di-isopropylethylamine was added to adjust the pH to 9 before the introduction of pentafluorobenzenesulfonyl chloride (45 mg, 0.17 mmol). This mixture was stirred for 16 h. The solvent was evaporated and the crude material treated in the standard procedure described in example one. Column chromatography (100% ethyl acetate to 10% methanol in ethyl acetate) afforded 33 mg (31%) of BocLys[$CO(CH_2)_3NHSO_2Pfp$]pyrrolidide as a colourless oil.

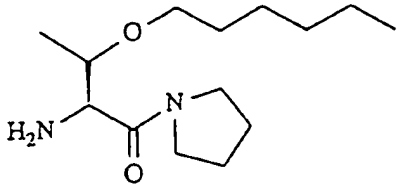
^{1}H NMR ($CDCl_3$), δ (ppm); 7.19 (1H, br.t, J = 6.3 Hz); 6.18 (1H, br.t, J = 6.6 Hz); 5.50 (1H, d, J = 8.4 Hz); 4.38 (1H, m); 3.65 - 3.16 (8H, m); 2.36 (2H, t, J = 6.8 Hz); 2.01 - 1.82 (8H, m); 1.69 - 1.41 (4H, m); 1.43 (9H, s).

This product was stirred in trifluoroacetic acid (10 cm^3) for 30 min. The solvent was evaporated and the residue dissolved in water, filtered and lyophilised to yield 30 mg of H-Lys[$CO(CH_2)_3NHSO_2$Pfp]Prl (110) as a colourless oil.

FAB Mass Spec: Calculated 514.2; Found $(M+H)^+$ = 515.2.

EXAMPLE FOUR

H-Thr[$(CH_2)_5CH_3$]pyrrolidide (143)



Pyrrolidine (0.88 g, 12.4 mmol) was added to a solution of BocThrONSu (3.0 g, 9.5 mmol) in dry CH_2Cl_2 (30 cm^3), under a nitrogen atmosphere. The reaction was stirred for 60 min at room temperature. The solvent was evaporated and the residue was treated in the standard procedure as described for example one. The residue was subjected to column chromatography (hexane:ethyl acetate, 30:70) to afford 2.50 g (96%) of 1-[N-(t-butoxycarbonyl)threonyl]pyrrolidine as a colourless oil.

^{1}H NMR ($CDCl_3$), δ (ppm); 5.52 (1H, d, J = 6.5 Hz); 4.30 (1H, d, J = 7.4 Hz); 4.16 (2H, m); 3.72 (1H, m); 3.46 (3H, m); 1.98 - 1.82 (4H, m); 1.43 (9H, s); 1.19 (3H, d, J = 7.1 Hz).

Sodium hydride (17 mg, 0.70 mmol) was added to a solution of 1-[N-(t-butoxycarbonyl) threonyl]pyrrolidine in dry THF, at 0°C, under a nitrogen atmosphere. The mixture was stirred at 0°C for 15 min before the introduction of n-hexyl iodide (200 mg, 0.94 mmol). The reaction was then allowed to stir at room temperature for 16 h. The solvent was evaporated and the residue treated in the standard manner as described in example one. The crude product was subjected to column chromatography (hexane:ethyl acetate, 40:60) to afford 25 mg (10%) of BocThr[$(CH_2)_5CH_3$]pyrrolidide (143).

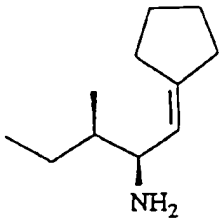
^{1}H NMR ($CDCl_3$), δ (ppm); 5.50 (1H, d, J = 6.9 Hz); 4.48 (1H, m); 3.70 - 3.32 (7H, m); 1.92 - 1.80 (6H, m); 1.52 (2H, m); 1.42 (9H, s); 1.30 (6H, m); 1.22 (8H, d, J = 6.9 Hz); 0.83 (3H, t, J = 7.9 Hz).

BocThr[$(CH_2)_5CH_3$]pyrrolidide (20 mg, 0.06 mmol) was stirred in 4N HCl/dioxan (5 cm^3) for 60 min. The solvent was evaporated, the residue taken up in water, filtered and lyophilised to yield H-Thr[$(CH_2)_5CH_3$]pyrrolidide (20 mg) as an orange oil. The product was purified by reverse phase HPLC to afford 15 mg of (143) as a colourless oil.

FAB Mass Spec: Calculated 256.2, Found $(M+H)^+$ = 257.3.

EXAMPLE FIVE

H-Ile-ψ[CH=CH]Pyrrolidide (149)



1.6 N ^{n}Butyl lithium (0.50 cm^3, 0.76 mmol) was added to a stirred solution of cyclopentyl triphenyphosphonium bromide (287 mg, 0.69 mmol) in dry THF (6 cm^3), under a nitrogen atmosphere, maintaining the temperature at -30°C. After stirring for 60 min, the solution was further cooled to -50°C subsequent to the dropwise addition of a solution of N-(t-butoxycarbonyl)-L-isoleucinal (125 mg, 0.58 mmol, prepared by the method of Fehrentz and Castro, *Synthesis*, 1983, 676), in dry THF (4 cm^3). After the final addition, the reaction was allowed to slowly attain room temperature, over 3.5 h.

The reaction was quenched with saturated ammonium chloride solution (2 cm^3). This was diluted with water (10 cm^3) and extracted with diethyl ether (3 x 20 cm^3). The combined ethereal layers were washed with water (10 cm^3), dried (Na_2SO_4) and evaporated to yield 187 mg (>100%) of crude product. Column chromatography (90:10, hexane:Et_2O) afforded 53 mg (34%) of Boc-Ile-ψ[CH=CH]pyrrolidide as a colourless oil.

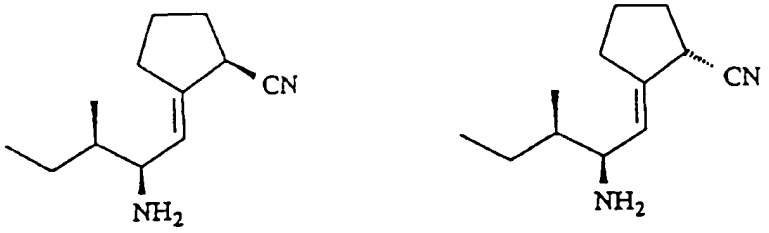
^1H NMR ($CDCl_3$), δ (ppm); 0.84 (3H, t, J = 6.9 Hz); 0.91 (3H, d, J = 7.3 Hz); 1.08 (1H, m); 1.44 (9H, s); 1.48 (1H, m); 1.64 (5H, m); 2.24 - 2.45 (4H, m); 4.08 (1H, br.s); 4.41 (1H, br.s); 5.12 (1H, dt, J = 2.3, 8.9 Hz).
^{13}C NMR($CDCl_3$) δ (ppm); 155.8, 147.4, 119.1, 79.2, 54.8, 40.1, 34.2, 29.6, 28.9, 26.8, 26.6, 26.1, 15.0, 12.1.

Treatment of this product with 4N HCl/dioxan for 35 min removed the Boc-protecting group. The reaction was evaporated, the residue dissolved in water, filtered and lyophilised to yield 24 mg (63%) of H-Ile-ψ[CH=CH]pyrrolidide (149) as a foamy solid.

FAB Mass Spec: Calculated 167.2, Found $(M+H)^+$ = 168.2.

EXAMPLES SIX AND SEVEN

H-Ile[(2R)-cyano-ψ(CH=CH)pyrrolidide] (150)
H-Ile[(2S)-cyano-ψ(CH=CH)pyrrolidide] (151)



N-(t-Butoxycarbonyl)-L-isoleucinal (2.40 g, 11.2 mmol) and 2-oxy-1-triphenyl-phosphoranecyclopentane (4.61 g, 13.4 mmol, prepared by method of H.O. House and H. Babed. *J. Org. Chem.*, 1963, 28, 90) were heated, at reflux, in toluene, under a nitrogen atmosphere. After 15 h, the mixture was cooled, and the solvent evaporated. Column chromatography (80:20, hexane:ethyl acetate) of the crude residue afforded 2.33 g (74%) of BocIle-ψ[CH=CH]pyrrolidin-2-one as a colourless oil.

^{1}H NMR ($CDCl_3$), δ (ppm); 6.29 (1H, dt, J = 2.6, 9.2 Hz); 4.59 (1H, br.d); 4.17 (1H, m), 2.82 (1H, m); 2.66 - 2.50 (2H, m); 2.34 (2H, t, J = 7.8 Hz); 1.96 (2H, q, J = 7.6 Hz); 1.44 (1H, m); 1.43 (9H, s); 1.12 (1H, m), 0.89 (3H, d, J = 5.3 Hz); 0.88 (3H, t, J = 6.9 Hz).

Diethylcyanophosponoacetate (0.30 cm^3, 1.92 mmol) was added to a solution of Boc-Ile-ψ[CH=CH]pyrrolidin-2-one (180 mg, 0.64 mmol) and LiCN (0.5 M in DMF, 3.84 cm^3, 1.92 mmol) in dry DMF (2 cm^3), under a nitrogen atmosphere. The reaction was stirred at room temperature for 30 min. The mixture was diluted with water (20 cm^3) and then extracted with ethyl acetate (2 x 30 cm^3). The combined organic layers were washed with water (5 x 10 cm^3), dried (Na_2SO_4) and evaporated to afford 360 mg (>100%) of crude product. A portion of this crude cyano-phosphonate (284 mg, 0.64 mmol) was dissolved in dry THF, and stirred under nitrogen. *tert*-Butanol (47 mg, 0.64 mmol) was added, followed by the dropwise addition of a solution of samarium (II) iodide (0.1 M in THF, 19.2 cm^3, 1.92 mmol). After the final addition, the reaction was stirred for a further 30 min before the addition of 2N HCl (20 cm^3). The mixture was extracted with diethyl ether (3 x 30 cm^3). The combined ethereal layers were washed with 10% $Na_2S_2O_3$ solution (10 cm^3), water (2 x10 cm^3) and brine (2 x 10 cm^3). The solution was dried (Na_2SO_4), evaporated and the crude residue subjected to column chromatography (90:10, hexane:ethyl acetate) to yield 122 mg (66%) of a diastereomeric mixture of Boc-Ile[2-(RS)-cyano-ψ(CH=CH)pyrrolidine] as a colourless oil.

^{1}H NMR ($CDCl_3$), δ (ppm); 5.52 (1H, d, J = 9.6 Hz); 4.5 (1H, br.s); 4.12 (1H, m); 3.35 (1H, m); 2.57 (1H, m); 2.38 (1H, m); 2.17 (1H, m); 1.91 (2H, m); 1.69 (2H, m); 1.53 (1H, m); 1.43 (9H, s); 1.12 (1H, m); 0.92 (1.5 H, d, J = 7.3 Hz); 0.91 (1.5 H, d, J = 7.3 Hz); 0.89 (1.5 H, d, J = 6.6 Hz); 0.86 (1.5 H, t, J = 6.9 Hz).

Treatment of this diastereomeric mixture with 4N HCl/dioxan for 60 min removed the protecting group. Evaporation of the solvent and subsequent reverse phase HPLC of the residue afforded the two pure diastereomers.

(150), (47 mg, 60%) FAB Mass Spec: Calculated 192.2, Found $(M+H)^+$ = 193.2
(151), (28 mg, 36%) FAB Mass Spec: Calculated 192.2, Found $(M+H)^+$ = 193.2.

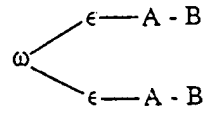
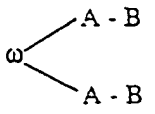
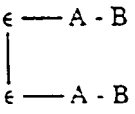
Preparative methods described herein in relation to Tables 1 - 8 and in examples one to seven form part of the present invention.

Abbreviations

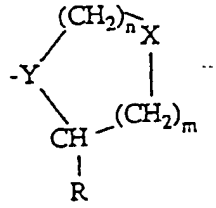
Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
BSA	Bovine serum albumin
^{n}Bu	*n*-Butyl
Ch	Cyclohexyl
DMF	Dimethylformamide
DMP	Dess-Martin Periodane
EDTA	Ethylenediaminetetraacetic acid
FAB	Fast atom bombardment
Gua	Guanidinyl
HPLC	High performance liquid chromatography
^{n}Hx	*n*-Hexyl
Mass Spec	Mass spectrometry
mCPBA	*meta*-Chloroperbenzoic acid
Mol Wt	Molecular weight
ONSu	N-O-Succinimide
Pfp	Pentafluorophenyl
Ph	Phenyl
Pip	Piperidyl
Prl	Pyrrolidide
Py	Pyridine
PyBop	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
WSCD	Water soluble carbodiimide
Z	Benzyloxycarbonyl

CLAIMS

1. Inhibitors of DP-IV mediated processes selected from those of general formula

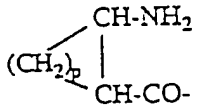
A-B (Groups I and II) and   and 

(Group III)

where B is 

n = 1 or 2;
m = 0, 1 or 2;
X = CH_2, O, S, SO, SO_2, NH or NR_1 where R_1 = lower alkyl (C_1 to C_5);
-Y = -N, -CH or =C (when the -CO group of A is replaced with -CH= or-CF=);
R = H, CN, CHO, $B(OH)_2$, C≡C-R_7, or CH=N-R_8 where R_7 = H, F, lower alkyl (C_1 to C_5), CN, NO_2, OR_9, CO_2R_9 or COR_9; R_9 = lower alkyl (C_1 to C_6); R_8 = Ph, OH, OR_9, $OCOR_9$ or OBn; A is attached to Y;
and wherein for the Group I compounds

(a) when R is H, A is an α-amino-acyl group derived from an α-amino-acid bearing a cycloaliphatic side-chain or is a β-amino-acyl group of general formula

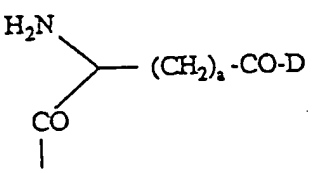
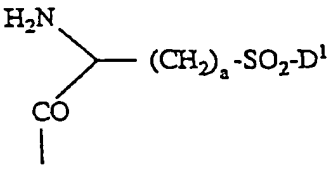


where p is 1 to 6, the ring in either case optionally having unsaturation and/or heteroatom substitution;

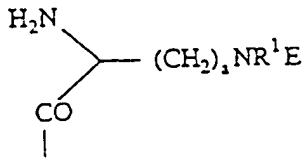
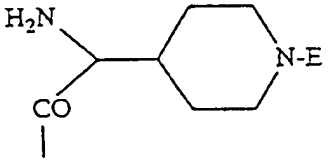
(b) when R = CN, C≡C-R_7 or CH=N-R_8, A is as defined at (a) and in addition may be derived from any L-α-amino acid bearing a lipophilic side-chain;

(c) and when R = CHO or $B(OH)_2$, A is a β-amino-acyl group as defined under (a);

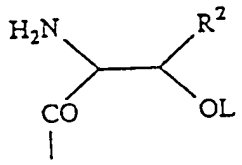
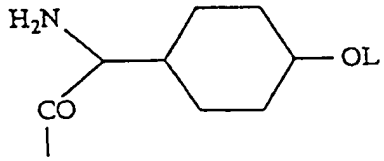
for the Group II compounds, R is H, CN, C≡C-R_7 or -CH=N-R_8 and A is

(i)  or 

where a = 1 - 5; D = -G-$(CH_2)_b$-$(R_4)_q$-R_3; G = O, NH or NMe; b = 0 - 12; q = 0 - 5; D^1 = D with G ≠ O; R_4 = Z-NH-$(CH_2)_c$- or NH-Z-$(CH_2)_c$- where c = 1 - 12 and Z = CO, CH_2 or SO_2; R_3 = CO_2H or ester thereof, $CONH_2$, $CONHNH_2$, $CONR_5R_6$, $CONHNR_5R_6$, PO_3H or ester thereof, SO_3H, SO_2NH_2, $SO_2NR_5R_6$, OH, OR_5, substituted or unsubstituted aryl or heteroaryl, NH_2, NR_5R_6, $NHCO_2R_5$, $NHSO_2NR_5R_6$, -$NHCOR_5$, NH-SO_2R_5, NH-CH(:NR_5)NR_5R_6, $NHCONR_5R_6$, sugar, CO-aminosugar, NHCO-aminosugar or -NHCS-aminosugar; and R_5 and R_6 are independently selected from H and lower alkyl, fluoroalkyl and cycloalkyl groups of up to 8 atoms and aryl, heteroaryl and alkyl heteroaryl groups of up to 11 atoms or R_5 and R_6 may together comprise a chain (C_3 to C_8); or is

(ii)  or 

where R^1 = H or Me, the ring may contain more heteroatoms, E = J-$(CH_2)_b$-$(R_4)_q$-R_3, J = CO, CH_2 or SO_2, and a, b, q, R_3 and R_4 are as defined under (i); or is

(iii)  or 

where R^2 = H or Me, the ring may contain one or more heteroatoms, and L = $(CH_2)_d$-$[CO]_r$-$(CH_2)_b$-$(R_4)_q$-R_3 or $(CH_2)_c$-NR^1-$(CH_2)_b$-$(R_4)_q$-R_3 where r = 0 or 1, d = 0 - 4, e = 2 - 4, and b, q, R_3 and R_4 are as defined under (i);

and for the Group III compounds, each B may have any identity defined therefor above, each A may be chosen from any Group II structure (i), (ii) or (iii) above with the terminal groups R_3 in the A residues replaced with a shared group -ϵ-ω-ϵ- or -ϵ-ϵ- or -ω-, and ϵ and ω are selected independently from CH_2, O, NH, CO, S, SO_2, Ph and NMe;

and wherein in Groups II and III at least one CH_2 group in a chain may be replaced by a bioisostere thereof or any amide group which connects A and B in a Group I, II or III compound or which is in a side-chain of A in a Group II or III compound may be replaced by an amide bioisostere.

2. An inhibitor of a DP-IV mediated process selected from examples 1 - 152 of Tables 1 to 8 herein.

3. The use of a compound according to claim 1 or 2 for the preparation of a medicament for inhibiting DP-IV mediated processes.

4. A method of treating or preventing disorder due to a DP-IV mediated process in a patient, which comprises administering to the patient a DP-IV inhibiting amount of compound according to claim 1 or 2.

5. A pharmaceutical composition containing a DP-IV inhibiting amount of compound according to claim 1 or 2.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 94/02615

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/16 C07D295/18 C07C211/25 C07C255/46 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 08259 (NEW ENGLAND MEDICAL CENTRE) 29 April 1993 see the whole document ---	1-5
A	WO,A,91 16339 (NEW ENGLAND MEDICAL CENTRE) 3 March 1993 cited in the application ---	1-5
A	DD,A,296 075 (MARTIN-LUTHER-UNIVERSITÄT HALLE) 21 November 1991 cited in the application see the whole document ---	1-5
A	DD,A,158 109 (MARTIN-LUTHER-UNIVERSITÄT HALLE) 29 December 1982 see examples 2-3 ---	1-5
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 1995	22. 03. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Kissler, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/GB 94/02615

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIOL. CHEM. HOPPE-SEYLER (1991), 372(5), 305-11 CODEN: BCHSEI; ISSN: 0177-3593, vol.372, May 1991 pages 305 - 311 Schoen, Ekkehard; Born, Ilona; Demuth, Hans Ulrich; Faust, Juergen; Neubert, Klaus; Steinmetzer, Torsten; Barth, Alfred; Ansorge, 'Dipeptidyl peptidase IV in the immune system. Effects of specific enzyme inhibitors on activity of dipeptidyl peptidase IV and proliferation of human lymphocytes' see RN 56414-88-1, Pyrrolidine, 1-(2-amino-4-methyl-1-oxopentyl)-, (S)- see RN 56414-89-2, Pyrrolidine, 1-(2-amino-1-oxo-3-phenylpropyl)-, ---	1-5
A	PATENT ABSTRACTS OF JAPAN vol. 1, no. 120 (C-77) (2929) 12 October 1977 & JP,P,52 083 749 (SHOWA) 12 July 1977 see abstract see RN 64964-11-0, Carbamic acid, [5-amino-6-oxo-6-(1-pyrrolidinyl)hexyl]-, 1,1-dimethylethyl ester, (S)- ---	1-5
A	FEBS LETT. (1993), 320(1), 23-7 CODEN: FEBLAL; ISSN: 0014-5793, vol.320, no.1, 1993 pages 23 - 27 Demuth, H. U.; Schlenzig, D.; Schierhorn, A.; Grosche, G.; Chapot-Chartier, M. P.; Gripon, J. C. 'Design of (.omega.-N-(O-acy 1)hydroxyamido)aminodicarboxylic acid pyrrolidides as potent inhibitors of proline-specific peptidases' -----	1-5

Form PCT/ISA 210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten ..al Application No
PCT/GB 94/02615

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9308259	29-04-93	CA-A- EP-A-	2121369 0610317	29-04-93 17-08-94
WO-A-9116339	31-10-91	EP-A-	0528858	03-03-93
DD-A-296075		NONE		
DD-A-158109		NONE		

INTERNATIONAL SEARCH REPORT

I. .national application No.
PCT/GB94/02615

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 4 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Lack of conciseness

The definition of the following substituent(s) is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:
A, B, e, w

The number of theoretically conceivable compounds resulting from the combination of all claimed substituents of above list precludes a comprehensive search. Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):
Examples 1-7
(Cf. Arts. 6, 15 and Rule 33 PCT. Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)